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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,909	09/17/2003	Brenda F. Baker	23546-07993/RTSP-0313US.P	8712

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/666,909	BAKER ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 9-17-03.

Claims 1-31 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of the claimed invention cannot be determined. The composition claimed comprises transfecting cells in the presence of a non-liposomal transfection agent, but, since the language is open ("comprises"), it is unclear whether the composition also optionally comprises a liposomal transfection agent. Appropriate clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions and methods for the transfection of bone marrow derived osteoclast precursor cells during early osteoclast differentiation comprising administration of a composition comprising an 8-80 nucleobase compound in the presence of a non-liposomal transfection agent, and which 8-80 nucleobase compound targets any nucleic acid molecule encoding RANK, and which compound shares between 70% and 100% identity with the target nucleic acid molecule encoding RANK. The specification and claims do not adequately describe the distinguishing features or attributes concisely shared by the members of the various and broadly claimed genera, which genera include *i*) non-liposomal transfection agents; *ii*) 8-80 nucleobase compounds sharing at least 70% identity with any nucleic acid encoding RANK; *iii*) osteoclast precursor cells in *early differentiation*.

The genus comprising 8-80 nucleobase compounds sharing at least 70% identity with any nucleic acid encoding RANK reads on a broad array of sequences (e.g. thousands of sequences), and the disclosure fails to provide a representative number of species for such a broad genus that provides for the function claimed, *i.e.* that inhibits expression of RANK and modulates differentiation of osteoclast precursor cells in early differentiation. The specification teaches the inhibition of mouse RANK (of SEQ ID NO. 3) expression in vitro comprising the administration of antisense oligonucleotides that are 20 nucleobases in length and share complete homology with mouse RANK of SEQ ID NO. 3. The specification teaches the in vitro transfection of osteoclast precursor

cells (RAW 264.7) and the subsequent inhibition of their differentiation following administration of the antisense oligonucleotide of SEQ ID No. 34 in combination with the non-liposomal reagent, FuGENE6. This antisense oligonucleotide (SEQ ID No. 34) that is fully complementary to a corresponding target region of the target mouse RANK gene of SEQ ID NO. 3 is not representative of the genus embracing 8-80 nucleobase compounds sharing at least 70% identity with any RANK target gene.

The genus encompassed by non-liposomal transfection agents is very broad and the disclosure fails to provide a representative number of species for such a broad genus that provides for the function claimed, *i.e.* that transfects bone marrow derived osteoclast precursor cells during early osteoclast differentiation. The specification teaches the transfection of osteoclast precursor cells RAW264.7 in vitro using FuGENE6 as the non-liposomal transfection agent. This is not representative of the broad genus comprising any non-liposomal transfection agents.

The disclosure does not clarify the common attributes encompassed by these very broad genera. Concise structural features that would distinguish structures within the broadly claimed genera of sequences, cells or compounds from those outside of the genera are missing from the disclosure. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the various genera claimed. Thus, Applicant was not in possession of the claimed genera.

Claims 1-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro transfection of osteoclast precursor cells (RAW 264.7) and the subsequent inhibition of their differentiation following administration of the antisense oligonucleotide of SEQ ID No. 34 in combination with FuGENE6, does not reasonably provide enablement for the successful targeting and modulation of target gene expression in vivo comprising the administration of the broadly claimed oligonucleotide structures, and further whereby differentiation is modulated in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods for the transfection and modulation of differentiation of bone marrow derived osteoclast precursor cells during early osteoclast differentiation comprising administration of a composition comprising an 8-80 nucleobase compound sharing at least 70% identity with any RANK target gene in the presence of any non-liposomal transfection agent.

The state of the prior art and the predictability or unpredictability of the art. The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The following references are cited herein to illustrate the state of the art of treatment in organisms that involves the delivery of nucleic acid molecules to appropriate cells in an organism. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids is a highly unpredictable endeavor due to target

accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo inhibition of target genes. (A. Branch, Trends in Biochem. Sci. 23: 45-50, *see* entire text for Branch; S. Crooke, Antisense Research & Application, Chapter 1, pp. 1-50, especially at 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using nucleic acid based approaches Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol.,14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: "It is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of ... oligonucleotides in vitro and in vivo (see Agrawal et al

especially at pages 79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic oligonucleotides to target cells).

See Opalinska (Nature Reviews, Vol. 1, pages 503-514, 2002) for a review of the unpredictabilities associated with the in vivo efficacy of double stranded oligonucleotides for target gene inhibition: "Although conceptually elegant, the prospect of using nucleic acid molecules for treating human malignancies and other diseases remain tantalizing, but uncertain." (3rd full paragraph on p. 503). "...it is widely appreciated that the ability of nucleic acid molecules to modify gene expression in vivo is quite variable, ant therefore wanting in terms of reliability." (1st full paragraph on p. 511).

The breadth of the claims and the quantity of experimentation required. The claims are broadly drawn to compositions and methods for the transfection and modulation of differentiation of bone marrow derived osteoclast precursor cells during early osteoclast differentiation comprising administration of a composition comprising an 8-80 nucleobase compound sharing at least 70% identity with any RANK target gene in the presence of any non-liposomal transfection agent.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues, whereby a representative number of the oligomeric compounds claimed, including the broad genus comprising any compound between 8-80 nucleobases sharing between 70% and 100% identity with

any target nucleic acid molecule encoding RANK, are delivered to the osteoclast precursor target cells in vitro or in vivo in adequate amounts, and further whereby RANK target gene expression is inhibited and osteoclast differentiation is modulated.

The specification and claims do not adequately describe the distinguishing features or attributes concisely shared by the members of the various and broadly claimed genera, which genera include *i*) non-liposomal transfection agents; *ii*) 8-80 nucleobase compounds sharing at least 70% identity with any nucleic acid encoding RANK; *iii*) osteoclast precursor cells in *early differentiation*.

Since the specification fails to provide any particular guidance for the successful targeting or delivery of a representative number of species of the broad genus of compounds claimed in vitro or in vivo, and further whereby the expression of any nucleic acid encoding a RANK target gene is inhibited, and differentiation is modulated, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of providing RANK target gene inhibition in vitro or in vivo using a representative number of species within the broad genus of compounds claimed. Applicants have not provided adequate written description for the compositions claimed, nor for the successful use of a representative number of species of the broadly claimed genera to provide RANK target gene inhibition and modulation of differentiation of osteoclasts in vitro.

The specification teaches the in vitro transfection of osteoclast precursor cells (RAW 264.7) and the subsequent modulation of their differentiation following administration of the antisense oligonucleotide of SEQ ID No. 34 in combination with the non-liposomal agent, FuGENE6. These experiments, however, are not representative or correlative of providing modulation of differentiation in vitro or in vivo using the broad genus of oligonucleotides claimed, nor of using the broad genus of non-liposomal transfection agents claimed.. One skilled in the art would not accept on its face the examples given in the specification of the in vitro targeting and inhibition and expression of mouse RANK using fully complementary antisense oligonucleotides as being correlative or representative of the successful inhibition of RANK expression or modulation of osteoclast differentiation in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the efficacy of administering candidate biological agents to any organism. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with delivery of nucleic acid agents to osteoclast precursor cells, and further whereby differentiation is modulated in vitro or in vivo using the broad genera claimed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94

(December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
4-26-06

TC 1600

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PRIMARY EXAMINER